REMARKS

Applicants respectfully request reconsideration of the present application in view of the following reasons.

Claims 15 and 24-28 are now pending in this application.

Written Description Rejections

Regarding claim 15, the rejection contends that the specification does not provide adequate written description support for the phrase "elevated blood levels of ionized calcium," which "requires the treatment of a patient suffering from elevated blood levels of ionized calcium asso[ci]ated with cachexia rather than the treatment of cachexia." Office Action mailed July 26, 2005, paragraph spanning pages 2-3. The rejection also asserts that "[o]ne of skill in the art upon reading the specification as filed would not have concluded that the method was confided to those individuals suffering from cachexia induced hyperglycemia as the specification clearly states the intention of treating cachexia." *Id.* The rejection further cites a reference (Harrison et al.) for the proposition that it was recognized in the art that hypercalcemia associated with malignancy is observed in patents who are a few months from death. Based on these assertions, the rejection concludes that the treatment of patients suffering from cachexia who exhibit high levels of blood calcium is not supported by applicants' specification or the claims as filed.

Applicants respectfully respond that Examples 2 and 3 (pages 24-27) of the specification do support the claim phrase "elevated blood levels of ionized calcium," as well as the phrase "elevated blood levels of ionized calcium accompanied by cachexia." Example 2 examines the effect of an anti-IL-6 receptor antibody on a cachexia mouse model, and specifically notes that "ionized calcium in the blood on day 11 was remarkably elevated in the tumor-bearing control group as compared to the non-tumor-bearing control group, whereas in the MR16-1 [anti-IL-6 receptor antibody] administration group, a significant suppressing effect was observed (Fig. 15)." Specification, page 25, line 36 – page 26, line 3. In other words, applicants expressly disclosed that an anti-IL-6 receptor antibody "suppress[ed] an elevation of blood levels of ionized calcium" as claimed.

In Example 3, applicants examined the effect of an anti-IL-6 receptor antibody "on the occ-1-induced cachexia model accompanied by hypercalcemia." Specification, page 26 lines 9-10. Thus, the specification expressly refers to hypercalcemia accompanied by cachexia. The specification goes on to teach that:

> There was a reduction in body weight [cachexia] in the tumor-bearing group, but the MR16-1 [anti-IL-6 receptor antibody] administration group has shown a similar changes in body weight as the non-tumor-bearing control group, indicating suppression of reduction in body weight [i.e., suppression of cachexia] (Fig. 17).
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> The concentration of ionized calcium in the blood was remarkably elevated in the tumor-bearing control group as compared to the non-tumor-bearing control group, whereas in the MR16-1 administration group the elevation was strongly suppressed (Fig. 18).

Specification, page 26, line 30 – page 27, line 2. Thus, the specification clearly discloses, via the mouse cachexia model, that one can treat/suppress elevated blood level of ionized calcium accompanied by cachexia using an antibody to an IL-6 receptor.

Applicants do not understand the relevance of the rejection's comments regarding "cachexia induced hyperglycemia" or how the Harrison reference in any way undermines the fact that the above-mentioned teaching is expressly disclosed in the specification. Applicants further point out that verbatim support is not required. *See* MPEP §2163, citing *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in ipsis verbis [i.e., 'in the same words'] to be sufficient").

Regarding claim 24, the rejection asserts that the specification fails to provide support for the "chimeric antibody" element recited in the claim. Applicants respectfully direct the Examiner's attention to page 8, lines 6-11 of the specification, which expressly discloses a chimeric antibody in the context of applicant's invention.

Obviousness Rejections

The Examiner has rejected claim 15 under 35 U.S.C. §103(a) as being unpatentable over Yoneda et al. (Cancer Research, 53: 737-40 (1993)) in view of Shimamura et al. (U.S. Pat. No. 5,639,455).

The Examiner suggests that Yoneda et al. teaches that administration of anti-IL-6 antibodies lowered blood calcium levels in mice with tumors associated with increased production of IL-6. The Examiner acknowledges Yoneda et al. does not teach the administration of anti-IL-6 receptor antibodies.

Yoneda et al. discusses the effect of an anti-IL-6 antibody (but not an anti-IL-6 receptor antibody) on hypercalcemia associated with cancer. This reference does not suggest that hypercalcemia is associated with cachexia, or that the anti-IL-6 antibody suppresses "elevated blood levels of ionized calcium accompanied by cachexia" as recited in the claimed method. While the reference provides data indicating that anti-IL-6 antibodies may reverse malignancy-associated hypercalcemia (*see* page 739, 2nd col, lines 29-31), it does not suggest that it reverses hypercalcemia accompanied by cachexia. In fact, this reference expressly teaches that their studies with anti-IL-6 antibodies regarding diminishing progression of cachexia "did not achieve statistical significance." Yoneda et al., page 739, 2nd col., lines 21-23; *see also* page 738, 2nd col., lines 6-8 ("It appeared that the human IL-6 antibodies prevented further progress of cachexia, although not statistically significant (Fig. 3)." Thus, Yoneda teaches away from the claimed invention.

A skilled artisan reading this reference would not expect that an anti-IL-6 antibody (much less an anti-IL-6 receptor antibody) could be used to treat a patient "suffering from an elevated blood level of ionized calcium accompanied by cachexia." Nothing in this reference indicates that the two phenomenons (elevated calcium and cachexia) are linked, or that an anti-IL-6 receptor antibody would effect elevated calcium accompanied by, i.e., linked to, cachexia.

In addition, applicants point out that it is important that Yoneda et al. did not teach the use of an anti-IL-6 receptor antibody at all, despite the fact that it clearly could have. *See, e.g.*, page 739, 2nd col., lines 23-25 (stating that "[o]thers have reported that the IL-6 antibodies or IL-6 receptor antibodies inhibit plasmacytoma growth *in vivo*"—noting other studies using both types of antibodies). Furthermore, the fact that an anti-IL-6 antibody may have blocked a particular IL-6-induced phenomenon (hypercalcemia) did not necessarily indicate that an anti-IL-6 receptor antibody would block that same phenomenon. Those

skilled in the art knew that blood contained soluble IL-6 receptors, in addition to IL-6 receptors present on cell membranes. Skilled artisans therefore understood that anti-IL-6 receptor antibodies might bind to soluble IL-6 receptors, rather than cell surface IL-6 receptors. Consequently, a skilled artisan would not have recognized that an anti-IL-6 receptor antibody would necessarily block IL-6-induced event in cells.

In addition, skilled artisans also knew that blood contained a larger amount of IL-6 receptor compared to that of IL-6 (pg/ml level). Thus, skilled artisans would have believed that the amount of anti-IL-6 receptor antibody necessary to block IL-6-induced signal transduction would have been greater than that of the anti-IL-6 antibody. Thus, prior to the present invention, one of ordinary skill would not have necessarily expected to see similar results with an anti-IL-6 receptor antibody as with an anti-IL-6 antibody.

In this connection, applicants also note that an anti-IL-6 antibody directly binds to IL-6 and inhibits binding of IL-6 to the IL-6 receptor. In this case, one of skill in the art would have believed that the IL-6 bonded with the anti-IL-6 antibody was scavenged from the body. On the other hand, an anti-IL-6 receptor antibody binds to an IL-6 receptor, and inhibits binding of IL-6 receptor to IL-6. In this case, because the anti-IL-6 receptor antibody caps the IL-6 receptor, IL-6 is accumulated and its concentration increases. The accumulated IL-6 competes with the anti-IL-6 receptor antibody, and lowers its functions. Therefore, a skilled artisan would have understood that the function/action of an anti-IL-6 antibody could have significantly differed from that of an anti-IL-6 receptor antibody.

The rejection alleges that Simuamura et al. "teaches that antibodies to Il-6 or antibodies to the Il-6 receptor can inhibit the binding of Il-6 to the Il-6 receptor." Office Action, page 3, lines 24-25; *see also* page 4, lines 7-8. The Examiner also asserts that this reference teaches the administration of a peptide that inhibits binding of IL-6 to the IL-6 receptor for, *inter alia*, the treatment of cancer cachexia.

Applicants note that there is no discussion or suggestion in Simuamura et al. with regard to elevated blood levels of ionized calcium at all, much less that elevated calcium

blood levels might be associated with cachexia, or that anti-IL-6 receptor antibodies might treat/suppress that elevated calcium in patients.

Applicants recognized that that Simuamura et al. mentions in passing that anti-IL-6 antibody and anti-IL-6 receptor antibody have been known to inhibit binding of IL-6 to its receptor (*see* col. 3, lines 20-24). This reference teaches, however, the use of a peptide that blocks binding between IL-6 and its receptor, as well as the use of an anti-IL-6 antibody (not an anti-IL-6 receptor antibody) to make that peptide. One skilled in the art would have understood that the mechanisms of action of a peptide would be totally different from that of an antibody, not only regarding specific binding properties, but also regarding any effect that the binding might have on IL-6 or IL-6 receptor function in a cell. In any event, nothing in this reference teaches the use of an IL-6 receptor antibody to make such a peptide.

Importantly, nothing in Simuamura et al. teaches or suggests the use of an anti-IL-6 receptor antibody to treat cachexia, much less elevated calcium levels associated with cachexia. In fact, the reference teaches away from using any known antibody raised against IL-6 or its receptor for treatment in humans. *See* col. 3, lines 20-40 (remarking on immune reactions against mouse antibodies, the only antibodies against IL-6 or IL-6 receptor known at the time).

Thus, this reference, either alone or in combination with Yoneda et al. did not teach that anti-IL-6 receptor antibodies could be used to treat/suppress elevated blood levels of ionized calcium, or even that cachexia was associated with, i.e., linked to, elevation of calcium blood levels.

The rejection also has rejected claims 15, 24 and 25 under 35 U.S.C. §103(a) as being unpatentable over Yoneda et al. and Shimamura et al., in view of Schwabe et al. (J. Biol. Chem., 10: 7201-09 (1994)). According to the Examiner, Schwabe et at. teaches that an IL-6 receptor antibody, PM-1, completely inhibited the binding of IL-6 to the IL-6 receptor, citing page 7204, 2nd col., lines 27-29.

As an initial matter, applicants point out that this reference mentions nothing about cachexia or elevated calcium blood levels at all. In addition, applicants note that elsewhere in

Schwabe et al., the authors state the "data strongly suggest that the IL-6R expressed in [] four [human tumor] cell lines must differ in their affinities for ^{125}I-IL-6." *See* page 7204, 2nd col., lines 3-5; *see also* page 7204, 1st col., lines 6-10. In other words, one skilled in the art would have expected that antibodies against IL-6 would act differently than antibodies against IL-6 receptor in human tumor cells lines. Thus, this reference adds nothing to cure the deficiencies of Yoneda et al. and Shimamura et al.

The rejection also has rejected claims 15, 24-28 under 35 U.S.C. §103(a) as being unpatentable over Yoneda et al., Shimamura et al. and Schwabe et al., in view of Tsuchiya et al. (U.S. Pat. No. 5,795,965). The Examiner acknowledges that Tsuchiya et al. only taught the chimeric or reshaped PM-1 antibody for "therapeutic" purposes, and that the use of chimeric or humanized antibodies could reduce immunogenicity otherwise seen with mouse antibodies. *See* Office Action, page 5, lines 4-10 Thus, this reference cannot cure the deficiencies of Yoneda et al., Shimamura et al. and and Schwabe et al.

For the reasons discussed above, applicants believes that the present application is now in condition for allowance. Favorable reconsideration of the application is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date 1/26/06

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